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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,277	12/21/2001	Timothy E. Benson	00481.CN1	3061

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EXAMINER
SMITH, CAROLYN L

ART UNIT	PAPER NUMBER
1631	9

DATE MAILED: 09/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,277	BENSON ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *19-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-25* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' elections with traverse of Group I (claims 1-18) and Specie E (a salt which is a combination of salts) and Specie F (a glycol which is PEG) in Paper No. 8, filed 6/11/03, are acknowledged. Claims 19-25 are withdrawn from consideration as being drawn to non-elected Groups.

Applicants' traversal is on the grounds that (1) the inventions as claimed can be readily evaluated in one search and (2) the generic claim includes sufficiently few species so that a search and examination of all species would not impose a serious burden on the Examiner.

The applicants' request to combine groups and species into one invention was found unpersuasive because of the following reasons (reiterated from the restriction paper):

The distinctness or independence of a sodium chloride versus ammonium sulfate versus magnesium sulfate versus lithium sulfate versus combination of salts (First specie election requirement for Group I) and PEG versus PEG-MME versus PEG-DME versus polyoxyalkylenepolyamines versus a combination of glycols (Second Specie Election Requirement for Group I) is because these species are separate chemical and entity types of the invention which are often separately characterized and published in literature, thus adding to the search burden if all species were examined together. Also, processing that may connect two species does not prevent them from being considered distinct because enough processing can result in the production of any composition from another composition as long as the processing is not limited in occurrences such as subtractions, additions, and enzymatic action. The distinctness of mammalian cells versus insect cells (Group II) and mammalian cell lines versus insect cell lines (Group III) is because these entities are from different phyla of organisms

containing distinctly different characteristics. Thus, the above-mentioned species are independent and/or distinct invention types for restriction purposes.

Inventions in Groups I, II, and III are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the crystalline polypeptide of Group II may be utilized in distinct usages as needed in Group I in a method for crystallizing a human beta secretase molecule or molecular complex, in a method of producing human beta secretase as in Group III, or alternatively, in a pharmaceutical composition. All of these usages are distinct as requiring distinct and different functions thereof without overlapping search due to different subject matter. This lack of overlapping searches documents the undue search burden if they were searched together.

The requirements are still deemed proper and are therefore made FINAL.

The information disclosure statements (IDSs), filed 3/7/02 and 9/12/02, fail to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP § 609, because references "BLAST 2 Sequences" and "Protein Data Bank" (in IDS, filed 3/7/02) as well as reference "Protein Data Bank" (in IDS, filed 9/12/02) lack publication dates on the actual copy, only a retrieval date was noted. They have been placed in the application file, but the information referred to therein has not been considered as to the merits. The Rossman, ed. reference (Intl. Sci. Rev., page 4 of 5 of the IDS, filed 3/7/02), the Wycoff et al. reference (Methods in Enzymology Vol. 114, page 5 of 5 of the IDS, filed 3/7/02), and the Wycoff et al. reference (Methods in Enzymology Vol. 115,

page 5 of 5 of the IDS, filed 3/7/02) were considered but were lined through because of their blurred citation. These references were added to the PTO-892 form (Notice of References Cited by Examiner) so that they will still be appropriately documented. (Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609, ¶ C(1).

The corrected drawings, filed 6/11/03, are accepted by the draftsperson.

Amendments in the specification, filed 6/11/03, to correct sequence compliance requirements are approved by the Examiner.

Claims herein under examination are 1-18.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, such as on page 18, line 20 and page 40, line 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v.*

Eagle Mfg. Co., 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-18 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 54-71 of copending Application No. 10/028224.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No. 10/144441. Application 10/144441 discloses a method for crystallizing a human beta secretase molecule or molecular complex in claims 1-23. While the scope of claim 1 of Application 10/144441 differs from instant claim 1 with the addition of crystallizing the human beta secretase molecule or molecular complex (claim 1, line 5 of Application 10/144441)

as well as stating the solution comprises of purified human beta secretase and the inhibitor with a pH of at most about 6.0 (claim 1, lines 6-7 of Application 10/144441), there is significant overlap between this claim of Application 10/144441 and the instant claim 1 as both methods crystallize a human secretase molecule or molecular complex which encompass similar inventions. The pH stated in instant claim 1 is also stated in claim 4 of Application 10/144441. Claims 1-18 of the instant application and claims 1-23 Application 10/144441 have differing scopes but contain significant overlap with minor obvious variations which suggests an obviousness-type double patenting issue.

This is a provisional obviousness-type double patenting rejection.

Claims 1-5, 7-8, and 10-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-23 and 25-26 of copending Application No. 10/143723. Application 10/143723 discloses a method for crystallizing a human BACE molecule or molecular complex in claims 12-23 and 25-26. Human BACE molecule as stated in claim 12 of Application 10/143723 is also known as human beta secretase as stated in the instant claim 1. While the scope of claim 1 of Application 10/143723 differs from instant claim 1 with the words "potential modifier" (claim 12, line 3 of Application 10/143723) which can mean an inhibitor or enhancer as well as stating the solution comprises human BACE and the modifier with a pH of 4.5 to 5.6 (claim 12, lines 5-7 of Application 10/143723), there is significant overlap between this claim and the instant claim 1 as both methods crystallize a human secretase molecule or molecular complex which encompass similar inventions. Overall, claims 1-5, 7-8, and 10-14 of the instant application and claims 12-23 and

25-26 of Application 10/143723 have differing scopes but contain significant overlap with minor obvious variations which suggests an obviousness-type double patenting issue.

This is a provisional obviousness-type double patenting rejection.

Claims 1-8 and 10-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-15 and 17-23 of copending Application No. 10/143502. Application 10/143502 discloses a method for crystallizing a human beta secretase molecule or molecular complex in claims 7-15 and 17-23. While the scope of claim 7 of Application 10/143502 differs from instant claim 1 with the words "potential modifier" (claim 1, lines 3-4 of Application 10/143502) which can mean an inhibitor or enhancer as well as stating the solution with a slightly different pH of 3.5 to 5.6 (claim 7, lines 5-6 of Application 10/143502), there is significant overlap between this claim and the instant claim 1 as both methods crystallize a human secretase molecule or molecular complex which encompass similar inventions. Overall, claims 1-8 and 10-16 of the instant application and claims 7-15 and 17-23 of Application 10/143502 have differing scopes but contain significant overlap with minor obvious variations which suggests an obviousness-type double patenting issue.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections – 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of the skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Although Applicants have disclosed information to enable one skilled in the art to make the trigonal space group $P3_221$ crystals of human beta secretase with (hexagonal shaped unit cells, page 6, lines 9-10) unit cell dimensions a =112.0 ± 35 Å, b = 112 ± 35 Å, c = 110 ± 35 Å, α

$= \beta = 90°$, $\gamma = 120°$; and space group $P32_21$ with cell constants a = 99.4 ± 35 Å, b = 99.4 ± 35 Å; c = 117 ± 35 Å; $\alpha = \beta = 90°$, $\gamma = 120°$; the specification does not reasonably provide enablement for crystallizing other human beta secretase molecules or molecular complexes as stated in claim 1. The claim is broader than the enablement provided by the disclosure with regard to the large number of possible crystalline helicases that could be made. As the science of protein crystallization is well known to be a trial and error procedure with unpredictable results (Drenth, page 1, lines 13-20), one skilled in the art would require clear and precise guidance to make any particular crystal. Accordingly, it would be very difficult for a skilled artisan to make crystal structures of other crystalline human beta secretases or co-complexes beyond those mentioned in the instant case where specific coordinates are disclosed. Due to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystals disclosed in the specification without undue experimentation. Also, the information provided in the Examples section, pages 33-44, does not sufficiently enable a skilled artisan to make compositions comprising crystalline human beta secretase as no specific chemical entities or ligands were mentioned. Again, due to the unpredictability in the art, a skilled artisan could not reasonably expect to make other human beta secretase crystallines or co-crystalline complexes based on generic guidelines without undue experimentation.

LACK OF WRITTEN DESCRIPTION

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-18 are directed to crystallizing a human beta secretase molecule or molecular complex. There is no disclosure regarding any crystals other than the trigonal space group $P3_221$ crystals of human beta secretase with unit cell dimensions a =112.0 ± 35 Å, b = 112 ± 35 Å, c = 110 ± 35 Å, $\alpha = \beta = 90°$, $\gamma = 120°$; and space group $P32_21$ with cell constants a = 99.4 ± 35 Å, b = 99.4 ± 35 Å; c = 117 ± 35 Å; $\alpha = \beta = 90°$, $\gamma = 120°$. As written, the claim may contain other crystals which do not meet the written description provision of 35 USC 112, first paragraph. Applicants have not sufficiently described other crystals and compositions in such full, clear, and concise terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims Rejected Under 35 U.S.C. § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 5, 9, 16, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 2 recites the phrase "the salt" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 5 recites the phrase "the glycol" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 5, 9, 16, and 17 are vague and indefinite due to the unclarity of citing an abbreviation, such as PEG, PEG-MME, PEG-DME, DMSO, CHO-K1, and HEK 293. Correction is suggested by amending in of the full name in parentheses.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-8, 10, and 13-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Hong et al. (Science, Vol. 290, 6 October 2000, pp. 150-153).

Hong et al. disclose crystallizing human memapsin 2 (also known as beta secretase) as a complex with an inhibitor, OM99-2 (p. 151, col. 1, lines 14-16 and col. 2, first paragraph; Figure 2; and p. 153, col. 2, References and Notes #11). Hong et al. disclose preparing a purified human beta secretase in the presence of an inhibitor using 0.2 M ammonium sulfate and 0.1 Na-cacodylate (p. 153, col. 2, References and Notes #12), which are a combination of salts with a concentration of about 0.001 M to about 0.5 M as stated in claims 2, 6, and 7. Hong et al. disclose crystallizing in a solution with a pH of 7.4 (p. 153, col. 2, References and Notes #12),

which is a pH of about 5.5 and about 4.7 as stated in claims 1 and 3, respectively. Hong et al. disclose using 22.5% polyethylene glycol (PEG) (p. 153, col. 2, References and Notes #12) as stated in claim 5, which is also about 40% by weight of the solution (as stated in claim 10) and about 5% to about 50% by weight of a glycol (as stated in claims 13 and 14). Hong et al. disclose the memapsin 2/OM99-2 complex crystals contain 56% solvent content (p. 153, col. 3, lines 2-5), which is about 40% by weight organic solvent as stated in claim 8.

Thus, Hong et al. anticipate the limitations in claims 1-3, 5-8, 10, and 13-14.

Claims 1-3, 5-15, and 17 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Tang et al. (P/N 6,545,127).

Tang et al. disclose methods for producing purified memapsin 2 (also known as human beta secretase, col. 3, line 23) and binding it to an inhibitor, OM99-2 for crystallization (col. 4, lines 8-9 and 22-33; Example 3). Tang et al. disclose crystallizing human beta secretase from a solution having a pH of 6.4 and 7.4 (col. 31, lines 1-4 and 40-43), which is a pH of about 5.5 and 4.7 as stated in claims 1 and 3, respectively. Tang et al. disclose using 0.1 M sodium cocadylate (col. 31, lines 2 and 41), and 0.2 M $(NH_4)_2SO_4$ in solution, which is a combination of salts with a concentration of about 0.001 M to about 0.5 M as stated in claims 2, 6, and 7. Tang et al. disclose using 30% and 22.5% polyethylene glycol (PEG) (col. 31, lines 1-2 and 42) as stated in claim 5, which is also about 40% by weight of the solution (as stated in claim 10) and about 5% to about 50% by weight of a glycol (as stated in claims 13 and 14). Tang et al. disclose a beta secretase concentration near 5 mg/ml (col. 30, lines 25-28) as stated in claim 11. Tang et al. disclose an inhibitor present at a concentration of 0.3 mM (col. 7, lines 41-42), which is about

0.1 mM to about 10mM as stated in claim 12. Tang et al. disclose human beta secretase was isolated from human pancreatic cells (col. 17, lines 16-55) as stated in claim 15. Tang et al. disclose memapsin 2 from HEK 293 cells (col. 8, lines 1-2) as stated in claim 17. Tang et al. disclose human beta secretase is found in multiple tissues, including pancreas, kidney, and ovary cells (col. 18, lines 8-18). Tang et al. disclose the memapsin 2 protein is expressed in a bacterial cell (claim 1). Tang et al. disclose the inhibition of memapsin 2 by OM99-1 in a 5% DMSO solution (Figure 4A and col. 5, lines 15-17), which is up to about 40% by weight organic solvent as stated in claims 8 and 9.

Thus, Tang et al. anticipate the limitations in claims 1-3, 5-15, and 17.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

August 25, 2003

ARDIN H. MARSCHEL
PRIMARY EXAMINER